

## REMARKS

### *Status of the Claims*

Claims 1-2, 6-11, 16-33, and 37-38 are pending. Claims 1, 2, and 37 are amended. Claims 34-36 are canceled without prejudice or disclaimer to the subject matter therein. Applicants reserve their right to file continuation application(s) directed to the canceled subject matter. Support for the amended and new claims can be found throughout the specification and in the claims as originally filed. *See, e.g.*, Specification, paragraphs [016], [043], and [045].

Applicants respectfully submit that the claim amendments reduce issues for appeal, do not raise issues that would require further consideration and/or search, and do not introduce new matter. Accordingly, Applicants respectfully request entry of the above amendments.

### *Withdrawn Rejections*

Applicants greatly appreciate the Examiner's withdrawal of the rejections under 35 U.S.C. §§ 101 and 102.<sup>2</sup>

#### *Claim Rejections - 35 U.S.C. § 112, First Paragraph (New Matter)*

Claims 1, 2, and 37 stand rejected under 35 U.S.C. § 112, 1<sup>st</sup> paragraph as allegedly failing to comply with the written description requirement. The Office Action objects to the recitation of "or other delivery system."<sup>3</sup>

Claims 1, 2, and 37 are amended to delete the recitation of "or other delivery system." Accordingly, Applicants submit this rejection is moot.

#### *Claim Rejections - 35 U.S.C. § 112, First Paragraph*

Claims 1, 2, 4, 6 and 16-31 stand rejected under 35 U.S.C. § 112, 1<sup>st</sup> paragraph, because the specification, while being enabling for a method of proliferating cardiomyocytes *in vitro* and *in vivo* comprising introducing nucleotide sequences coding for a nuclear localization signal, D-type cyclin gene (D1, D2, or D3) and a cyclin dependent kinase gene (CDK4 or CDK6) directly into the cardiomyocytes using an adenoviral expression vector, allegedly does not reasonably provide

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<sup>2</sup> See Office Action, pages 3 and 4.

<sup>3</sup> See *id.* at pages 2 and 3.

enablement for a method of proliferating cardiomyocytes using any delivery system for introducing the required nucleotide sequences.<sup>4</sup>

Applicants respectfully disagree and traverse this rejection.

As an initial matter, Applicants point out that claims 1, 2, and 37 are amended to delete the recitation of “or other delivery system.” Claims 1 and 37 are also amended to recite that the nucleotide sequences are introduced directly into the cardiomyocytes.

Applicants also provide the following comments.

**A. The Office Action Fails To Establish A *Prima Facie* Enablement Rejection**

The Office Action contends that “any vector or any viral vector would not predictably provide sufficient directed delivery and expression of the cyclin and CDK genes, absent further undue experimentation.”<sup>5</sup>

Applicants respectfully disagree and submit that the Office Action fails to establish a *prima facie* case of enablement. Indeed, the Office Action does not provide any evidence for the above-quoted assertion.<sup>6</sup> As is well established, the bare assertion of unpredictability is legally insufficient to make out a *prima facie* case of non-enablement.<sup>7</sup> Accordingly, for at least this reason, Applicants request that the rejection be withdrawn.

**B. The Full Scope Of The Claimed Invention Is Enabled**

The claimed invention is directed to methods of proliferating cardiomyocytes comprising administering various nucleic acids directly into cardiomyocytes using a vector.

Applicants submit that the evidence of record and that cited herein demonstrates that the use of vectors in the claimed invention are enabled. First, as the Office Action acknowledges, the

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<sup>4</sup> Applicants greatly appreciate the Examiner’s indication that the scope of enablement is expanded to include a method of proliferating cardiomyocytes *in vivo*. See Office Action, page 4.

<sup>5</sup> Office Action, page 5.

<sup>6</sup> The Office Action previously cited Tamamori-Adachi et al. and Nicol et al. to support an assertion that the art is unpredictable, but this assertion did not in any way relate to vectors. Applicants addressed these references in its prior response. See Applicants’ response, filed April 4, 2008, pages 8 and 9.

<sup>7</sup> See *Ex Parte Goedel*, 5 USPQ 2d 1449, 1450 (PTO Bd App. & Int. 1987) (“Mere broad generalizations and allegations are insufficient for holding of non-enablement.”)

specification teaches the use of an adenoviral vector.<sup>8</sup> Second, the specification discloses the use of vectors other than adenoviral vectors (e.g., viral vectors).<sup>9</sup> Third, the specification teaches that a nuclear localization signal is added to direct delivery and expression of the cyclin and CDK genes.<sup>10</sup> Fourth, Applicants submit that the state of art establishes that the use of vectors is enabled. Indeed, the USPTO has granted numerous patents directed to cardiovascular-related methods comprising administering any vector comprising a nucleic acid to an individual (e.g., human):

- U.S. Patent No. 5,661,133 — directed to methods of expressing a protein in cardiac myocytes comprising injecting into a mammalian host an expression vector comprising DNA encoding a protein that induces angiogenesis.<sup>11</sup>
- U.S. Patent No. 5,797,870 — directed to methods of treating a patient's heart comprising injecting into the heart a vector including DNA encoding a therapeutically useful protein;<sup>12</sup>
- U.S. Patent No. 5,883,082 — directed to methods of treating allograft rejection in an allograft recipient comprising treating with an oligonucleotide targeted to a nucleic acid sequence encoding various molecules.<sup>13</sup>
- U.S. Patent No. 6,199,554 — directed to methods of enhancing injury-induced revascularization of a tissue as a treatment of a disease comprising injecting into said tissue a nucleic acid molecule encoding a revascularization-promoting molecule.<sup>14</sup>

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<sup>8</sup> See, e.g., Specification, Example 5; see also Office Action, page 5 (“...the instant specification exemplifies the delivery of the cyclin and CDK genes via an adenoviral expression vector...”).

<sup>9</sup> See, e.g., Specification, ¶¶ [045]-[046]; see also Office Action, page 2 (“...the specification discloses several modes of gene delivery (microinjection, liposome, calcium phosphate transfection and viral)...”).

<sup>10</sup> See, e.g., Specification, ¶ [043].

<sup>11</sup> See, e.g., Claims 4, 8 (rous sarcoma virus vector), 12 (mammalian host is a human), and 13-16 (human suffers from a variety of cardiac diseases).

<sup>12</sup> See, e.g., Claims 16, 17, and 18 (vector is selected from the group consisting of retroviral vectors, adenovirus vectors, Herpes Simplex Virus vectors, Semliki Forest Virus vectors, and Sindbis virus vectors).

<sup>13</sup> See, e.g., Claims 18 and 22 (allograft is a cardiac allograft).

<sup>14</sup> See, e.g., Claims 1, 9 (nucleic acid molecule is naked DNA), 12 (viral vector), 13 (retrovirus, adenovirus, adeno-associated virus, or lentivirus), 15 (tissue is cardiac muscle), and 17 (disease is coronary artery disease).

- U.S. Patent No. 6,224,584 — directed to (i) a method for performing gene therapy in tissue of a patient's heart comprising contacting the heart wall with a gene therapy agent; and (ii) methods for inducing angiogenesis within the patient's heart wall comprising depositing a gene therapy agent within the patient's heart wall.<sup>15</sup>
- U.S. Patent No. 6,309,370 — directed to methods for intracardiac drug administration comprising administering to the heart a therapeutic drug comprising DNA.<sup>16</sup>
- U.S. Patent No. 6,316,419 — directed to methods for inducing collateral blood vessel formation in an animal heart, improving abnormal cardiac function in a mammal, and improving contractility of heart muscle in a mammal comprising injecting into heart muscle an expression vector comprising DNA encoding a protein that induces angiogenesis.<sup>17</sup>
- U.S. Patent No. 6,436,908 — directed to methods of inhibiting the activity of a beta adrenergic receptor kinase 1 (BARK1) so as to improve myocardial function in a mammal comprising administering to the cardiac muscle an expression vector comprising DNA encoding a BARK1 inhibitor.<sup>18</sup> and
- U.S. Patent No. 6,635,249 — directed to methods for treating or preventing congestive heart failure in a mammal comprising administering a polypeptide to said mammal.<sup>19</sup>

Patents are presumed valid.<sup>20</sup> As such, the claims of the above-identified patents are presumed to be based on a fully enabling disclosure as required by 35 U.S.C. § 112, first paragraph.<sup>21</sup> Accordingly, Applicants submit that these patents, in addition to the teachings in the specification,

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<sup>15</sup> See, e.g., Claims 2, 3, 5 (gene therapy agent is a vector containing a DNA segment capable of expressing an angiogenesis agent), and 6 (adenovirus vector).

<sup>16</sup> See, e.g., Claims 52, 74 (therapeutic drug comprises administering naked DNA), 75 (therapeutic drug comprises administering plasmid DNA), and 76 (therapeutic drug comprises administering adenoviral vector).

<sup>17</sup> See, e.g., Claims 1-3, 10 (mammal is a human), 11-13 (human suffers from a variety of cardiac diseases), and 15-16 (expression vector is a non-infectious vector).

<sup>18</sup> See, e.g., Claims 1, 4 (replication defective viral vector), 5 (replication defective adenoviral vector), and 6 (non-viral vector).

<sup>19</sup> See, e.g., Claims 1, 3 (mammal is a human), and 19 (said polypeptide is administered by administering an expression vector encoding said polypeptide).

<sup>20</sup> 35 U.S.C. § 282.

<sup>21</sup> See *Ex parte Goldhaber*, 41 USPQ2d 1172, 1175 (Bd. Pat. App. & Int. 1995) (citing *In re Lamberti*, 545 F.2d 747, 751 n.2, 192 USPQ 278, 281 n.2 (CCPA 1976); *In re Jacobs*, 318 F.2d 743, 137 USPQ 888 (CCPA 1963); *In re Michalek*, 162 F.2d 229, 74 USPQ 107 (CCPA 1947)).

provide adequate evidence to rebut the Office Action's unsupported assertion that the use of vectors in the claimed invention is not enabled.

**C. The Purported Issues Relating To Adenoviral Vectors Are Moot**

The Office Action asserts that "issues relating to cytotoxicity of adenoviral vector[s] delivered systemically have been previously made of record."<sup>22</sup> The Office Action, however, also indicates that the scope of enablement is expanded to include a method of proliferating cardiomyocytes *in vivo* comprising introducing an adenoviral expression vector. Accordingly, to the extent any "issues relating to cytotoxicity of adenoviral vectors" were previously raised, Applicants submit that the expanded scope of enablement renders these issues moot.<sup>23</sup>

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph.

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<sup>22</sup> Office Action, page 5.

<sup>23</sup> Applicants note that the prior Office Action cited Patel et al. for the proposition that adenoviral methodology of gene transfer in animals is complex and does necessarily equate with "success" in humans. Applicants responded by showing that Patel's own data "demonstrate the safety of direct myocardial administration of [an adenovirus vector] and **support the potential use of this strategy to treat human myocardial ischemia.**" (emphasis added). See Patel et al., Abstract; see also Applicants' response, filed April 4, 2008, page 8.